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Evaluation of dry eye parameters in patients with conjunctival papilloma following surgical excision with adjuvant mitomycin-C

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ABSTRACT

Aim: To evaluate the changes in tear osmolarity levels, tear function tests, and dry eye symptom scores in patients with conjunctival papilloma following surgical excision with adjuvant Mitomycin C (MMC).

Material And Method: Thirty patients diagnosed with conjunctival papilloma were enrolled in the study. Tear osmolarity, fluorescein break-up time (FBUT), Schirmer I test and eyelid margin score were evaluated at baseline and 1st, 3rd, and 6th months after conjunctival surgery with adjuvant 0.02% MMC were recorded. Dry eye symptom questionnaire scores obtained preoperatively and at the 1st, 3rd, and 6th months after surgery were also recorded. The mean values of test results noted at each control visit were compared.

Results: The mean age of the study population was 37±9.5 years. Schirmer I test scores, FBUT values, dry eye symptom scores, eyelid margin scores, and tear osmolarity values showed a significant difference between the preoperative measurements and follow-up visits ($p<0.05$). This difference was more apparent at the postoperative 1st-month visit. Measurement values showed that dryness peaked at the postoperative 1st month and gradually decreased afterward reaching the preoperative values at the postoperative 6th-month visit.

Conclusion: This study showed that conjunctival papilloma surgery with MMC is associated with transiently increased dry eye symptom scores and abnormal tear function tests.

Keywords: Conjunctival papilloma, Mitomycin C, tear osmolarity, dry eye disease

INTRODUCTION

Conjunctival papilloma is an acquired benign tumor that originates from the conjunctival stratified squamous epithelium. HPV infection is reported as the main risk factor which has 44-92% detection rates in the lesions (1). Conjunctival papillomas are encountered more commonly in men between the ages of 21 and 40 years with a progressive decrease in the incidence thereafter (2,3).

Various medical and surgical approaches have been described in the management of conjunctival papillomas (4). "No-touch" wide resection of the conjunctival lesions has been the traditionally performed method (5). Still, recurrences can be encountered after excision which can result in more severe conjunctival proliferations than the original lesions (6). For this reason, Mitomycin C (MMC) is commonly administered intraoperatively as an adjuvant agent to prevent recurrences (4).

Dry eye disease (DED) is characterized by the loss of homeostasis of the tear film accompanied by ocular symptoms (7). Objective evidences of DED are; reduced tear breakup time (TBUT), lower Schirmer score without topical anesthesia, and increased tear osmolarity measurements. Tear osmolarity measurement technology recently became available and the results showed increased osmolarity in all subtypes of DED with good sensitivity and specificity (8,9).

There have been several reports on the effect of MMC use for conjunctival papilloma excision (2-4). However, no known studies have described the development and course of DED in patients undergoing conjunctival papilloma excision with adjuvant MMC. In this study, we evaluated the changes in tear osmolarity levels, tear function tests, and dry eye symptom scores in patients with conjunctival papilloma following surgical excision with adjuvant MMC.

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MATERIAL AND METHOD

Thirty patients (12 female and 18 male) who underwent conjunctival papilloma excision surgery and completed 6-month follow-up visits between September 2020 and November 2022 at our Ocular Oncology Unit were retrospectively involved in this study design. Approval for the study was granted by the local Ethics Committee of our hospital with permit number (Date: 14/12/2022, Decision No: E1-22-3044). All procedures were carried out by the ethical rules and the principles of the Declaration of Helsinki. Hospital medical records and patient charts were reached to collect the study data. Patients with any serious systemic disease (e.g., primary Sjögren's syndrome), vitamin B12 deficiency, pregnancy, breastfeeding, history of smoking, current drug use, active ocular infection or allergy, previous ocular surgery, and use of contact lenses were excluded. Patients with recurrent diseases were also excluded.

Each patient preoperatively underwent a complete eye examination. Fluorescein break-up time (FBUT) testing, Schirmer I test (without anesthesia), eyelid margin score, tear osmolarity, and Ocular Surface Disease Index (OSDI) test scores were evaluated at baseline, and at the 1st, 3rd, and 6th months after surgery. For FBUT, a fluorescein strip moistened with preservative-free saline solution is applied to the inferior palpebral conjunctiva. The time passed between a blink and the appearance of the first dark spot is measured through the cobalt blue filter of the slit lamp. For Schirmer I test, a standard 5x35 mm strip of Schirmer paper was placed at the junction of the middle and lateral one-third of the lower eyelids. Patients were asked to keep their eyes closed. After 5 minutes, the strips were removed and the length of wetting was recorded. Eyelid margin score was noted on a 0-3 scale and the evaluation was as follows: eyelid margin irregularity (presence/absence), vascularity of the eyelid margin (presence/absence), occlusion of glands at the lid margin (presence/absence), and displacement of the mucocutaneous junction (presence/absence). All measurements were performed in the same order in the same examination room by the same examiner (CB). The OSDI questionnaire has 12 questions about individuals' ocular and visual symptoms in general, performance in certain activities, and certain weather conditions. Responses were evaluated on a scale of 0 to 4. A final score is calculated which ranges from 0 to 100 with scores 0 to 12 representing normal, 13 to 22 representing mild dry eye disease, 23 to 32 representing moderate dry eye disease, and greater than 33 representing severe dry eye disease (10).

As a rule, a 'No-touch' wide resection principle is followed for the surgical management of conjunctival papilloma cases at our center. The procedure is done under monitored anesthesia care with a regional block. Conjunctival forceps and blunt scissors are used for excision while extra care is taken not to touch the tumor. The lesion base is always cauterized after excision. Next, a 2x5-mm sponge soaked in a solution of 0.02% MMC is placed over the exposed sclera. The conjunctiva and tenon capsule are then pulled over the sponge with forceps, and the sponge is held in contact with the tissues for 5 minutes. Afterward, the sponge is removed and the ocular tissue is irrigated with saline solution. Primary closure with conjunctival advancement is performed. Topical antibiotic ointment and steroid drops are prescribed to be instilled every 6 hours daily. Steroid drops are tapered and discontinued after 2 weeks. Topical antibiotic drops are ceased after 1 week. Sutures are removed in the first week after the surgery. Follow-up examinations are performed on days 1, 7, 15, and 30, and then the 3rd and 6th months. Each visit covers a complete eye examination and an OSDI questionnaire filled out by the patient. All results are included in the patient's medical charts.

Data analysis was performed using the IBM SPSS 25.0 (Armonk, NY: IBM Corp.) statistical package program. Descriptive statistical methods (frequency, percentage, mean, standard deviation, median, and min-max) were used when evaluating the data. The conformity of the data to the normal distribution was evaluated by Kolmogorov-Smirnow and Shapiro-Wilk tests, skewness-kurtosis, and graphical methods (histogram, Q-Q Plot, Stem and Leaf, Boxplot). Repeated Measures Anova Test (repeated measures analysis of variance) was used for the comparison of repeated measurements. Post-hoc analysis was also performed to detect the significant differences between the measurements in different time intervals. The statistical significance level was accepted as $p=0.05$.

RESULTS

Thirty patients (12 female, 18 male) with a mean age of 37±9.5 years were enrolled. Schirmer I test scores, FBUT values, dry eye symptom scores, eyelid margin scores, and tear osmolarity values were compared between the baseline measurements and the follow-up visits after surgery (**Table** 1).

A statistical difference was found for FBUT and Schirmer I test results at the 1st and 3rd month visits and other measurement times; thus, 1st month values were the lowest ($p<0.05$). Similarly, tear osmolarity comparisons revealed increased osmolarity at the 1st and 3rd month visit, the 1st month being the highest ($p<0.05$). Both FBUT, Schirmer I test and tear osmolarity results showed that dryness peaked in the 1st month after surgery and gradually resolved to reach the preoperative values at

the 6th month visit after surgery. Eyelid margin scores also showed the same monthly pattern as the test results mentioned above, pointing to increased dryness after papilloma excision reaching the highest level in the 1st month followed by the 3rd month (p<0.05).

Table 1. Comparison of the preoperative and postoperative mean values of the dry eye parameters

Test	Mean±SD
Fluorescein Break-up Time (seconds)	
Preoperative 1	12.8±1.6
Postoperative	
1. month 2	9.7±2.0
3. month 3	11.4±1.8
6. month 4	12.4±1.3
P*	<0.001
Difference present between	2 and 1-3-4 3 and 1-2-4
Tear Osmolarity (mOsm/L)	
Preoperative 1	305.8±13.4
Postoperative	
1. month 2	324.5±9.1
3. month 3	316.1±17.8
6. month 4	308.7±19.1
P*	<0.001
Difference present between	1-4 and 2-3
Eyelid Margin Score	
Preoperative 1	1.0±0.7
Postoperative	
1. month 2	1.9±0.9
3. month 3	1.3±0.8
6. month 4	1.0±0.5
P*	<0.001
Difference present between	2 and 1-3-4 3 and 2-4
Schirmer I (mm)	
Preoperative 1	13.6±2.1
Postoperative	
1. month 2	10.3±1.9
3. month 3	11.9±1.6
6. month 4	13.1±1.6
P*	<0.001
Difference present between	2 and 1-3-4 3 and 1-2-4
OSDI Symptom Score	
Preoperative 1	13.5±0.9
Postoperative	
1. month 2	15.2±1.2
3. month 3	13.7±0.7
6. month 4	11.9±0.7
P*	<0.001
Difference present between	2 and 1-3-4 4 and 1-2-3

*: Repeated Measures Anova Test (Mean±SD)

OSDI scores were also found to be significantly higher at the 1st month visit than the preoperative scores (p<0.05). The mean OSDI score was found to be indistinctive of the preoperative mean value at the 3rd month visit, plus, 6th month visit mean OSDI value was even found to be significantly lower than the preoperative mean OSDI value (p<0.05). Graphs showing FBUT, Schirmer test results, tear osmolarity, dry eye symptoms and eyelid margin scores change over time were represented in **Figure 1**.

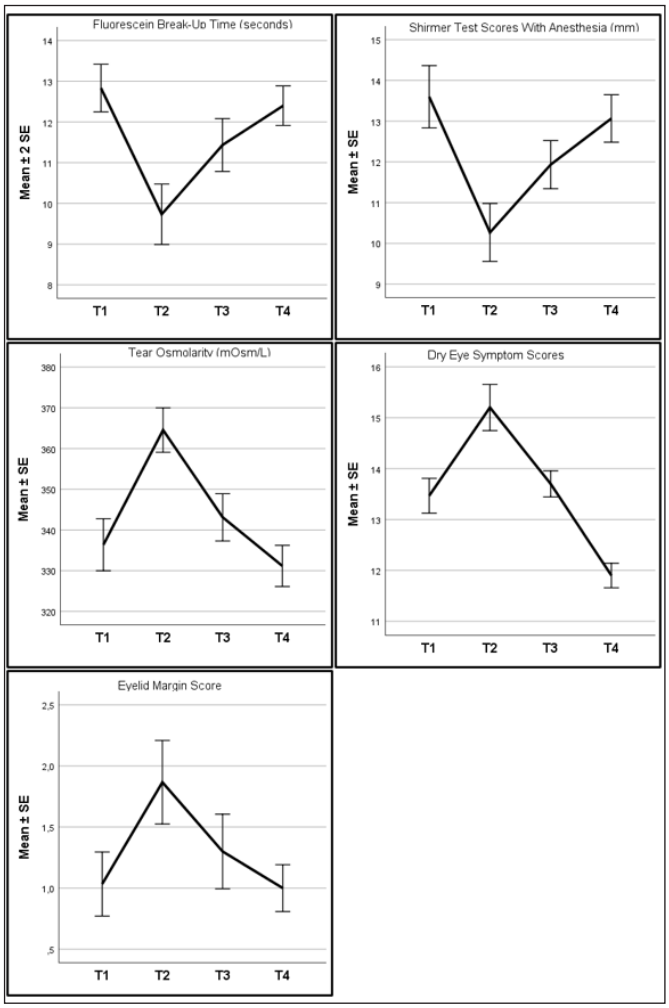

Figure 1. Graphs showing fluorescein break-up time, schirmer test results, tear osmolarity, dry eye symptom, and eyelid margin scores change over time

DISCUSSION

Conjunctival papilloma patients can have symptoms depending on the size and location of the tumor. Although smaller lesions are usually asymptomatic, larger lesions may cause foreign body sensation and dryness due to inadequate eyelid closure and chronic mucus production (1).

In this study, it was detected that conjunctival papilloma excision with MMC is associated with a transient increase in tear osmolarity and abnormal tear film function tests.

Before its use in ocular surface neoplasia, MMC had been widely used in glaucoma and pterygium surgeries for its antiproliferative effect on subconjunctival fibroblasts. MMC is considered a safe chemotherapeutic agent in treating ocular surface neoplasia. Transient side

effects including tearing, ocular pain, blepharospasm, keratoconjunctivitis, conjunctival hyperemia, and punctate epithelial keratopathy are common (11). Complications and side effects of MMC, when used in different surgical procedures, arise from direct contact of the MMC with the ocular surface. The effect of MMC use in photorefractive keratectomy had been evaluated previously and it was found that adjuvant MMC did not cause any exacerbation in dry eye symptoms (12). However, to our knowledge, no study had previously evaluated the effect of MMC use on tear function tests and dry eye symptom scores in conjunctival papilloma patients.

Tear osmolarity contributes to the pathogenesis of ocular surface damage and its measurement is one of the most objective parameters of DED. Increased tear osmolarity triggers inflammatory changes that may result in damage to the epithelial surface of the cornea and the conjunctiva (13). Tear osmolarity threshold values might vary from 305mOsm/L to 316mOsm/L, depending on the research (8,14,15). Currently, most researchers believe that the 316mOsm/L threshold better discriminates between mild and moderate-severe dry eye, while the 308mOsm/L threshold is widely accepted as the most sensitive value for discriminating between normal eyes and those presenting with early stages of the disease (14, 16). TearLab osmometer (TearLab, San Diego, CA, USA) reliability studies also revealed a sensitivity of 81% and a specificity of 80% when using the threshold value of 308 mOsml/L (17). In this study, we found that the mean preoperative osmolarity value was in the normal range. However, the mean osmolarity value reached 324.5±9.1 mOsm/L at the 1st month visit after surgery which is a value accepted to indicate severe DED. At the 3rd month visit mean osmolarity value was found to be lower (316.1±17.8 mOsm/L) than the 1st month value but still indicated moderate DED. Moreover, mean osmolarity returned to the normal cut-off value at the 6th month which is statistically not different than the mean preoperative value. These findings with tear osmolarity were further supported and reflected by TBUT, Schirmer I test, and eyelid margin score results. All tests revealed that DED peaked at the 1st month after surgery with a gradual decrease thereafter and a relative resemblance to preoperative values at the 6th month postoperatively.

OSDI questionnaire is used in this study to assess dry eye symptoms. We found that the mean OSDI score significantly increased in the 1st month after surgery and there was a continuous decrease in the next follow-up visits. At the postoperative 6th month visit, the OSDI scores were even detected to be significantly lower than the preoperative values. Although the OSDI questionnaire is not frequently used in the evaluation of patients with conjunctival papillomas, significantly higher OSDI scores in patients with pterygium compared to healthy controls had been previously reported (18,19). It was also shown that eyes with pterygium had significantly higher tear osmolarity levels than control fellow eyes without pterygium (20,21). Like pterygium, papilloma is an ocular surface proliferative disease associated with conjunctival inflammation. On the other hand, conjunctival papillomas are generally smaller and they are associated with less conjunctival inflammation than pterygium cases. Therefore, we found that conjunctival papilloma cases were associated with similar tear osmolarity levels, tear function tests, and OSDI scores with the normal population preoperatively. Our study results indicate that adjuvant MMC caused a secondary imbalance in the tear content which peaked in the postoperative first month. However, this effect was temporary and the test results returned to preoperative state at the postoperative 6th month. Still, care should be taken for the development of DED in these patients, even if minimum MMC is used intraoperatively.

Limitations of the study are the retrospective design and the limited number of patients. A prospective study evaluating tear parameters in conjunctival papilloma patients undergoing excision surgery with and without MMC would better reflect the effect of MMC. However, all papilloma surgeries are done with MMC at our center to prevent recurrences and we were not able to enroll a control group due to the retrospective design. Still, our study provides a valuable contribution to the literature about the changes in tear osmolarity levels, tear function tests, and dry eye symptom scores in patients with conjunctival papilloma following surgical excision with adjuvant MMC.

CONCLUSION

This study showed that conjunctival papilloma-affected eyes were associated with similar tear osmolarity levels and tear function tests with the normal population preoperatively. It was also determined that MMC applied to the conjunctiva during surgery negatively affected the ocular surface causing increased tear osmolarity and diminished tear function tests. Nevertheless, DED signs and symptoms and osmolarity values decreased through the follow-up period which indicates that the effect of MMC use during papilloma excision surgery is temporary.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Ethics Committee (Date: 14/12/2022, Decision No: E1-22-3044)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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